Refer to: Fitzgerald F: The great imitator, syphilis—Medical Staff Conference, University of California, San Francisco. West J Med 134:424-432, May 1981

The Great Imitator, Syphilis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. TIERNEY:* *The topic of this medical staff conference is the "great imitator," syphilis. Dr. Faith Fitzgerald, a University of California, San Francisco, alumna who has recently returned to California after a two-year absence, will discuss this disease of increasing importance.*

DR. FITZGERALD:† Between the 15th and 17th centuries, waves of pestilence swept Europe, decimating populations. The Black Death, bubonic plague, persists today but only in pockets. Typhus and typhoid have been largely eliminated by modern hygiene. Smallpox is, at last, a conquered disease. But greatpox, syphilis (so called because it was so much more dreadful than smallpox), is still epidemic among us.

Apocrypha has it that the sailors of Columbus brought gonorrhea to the New World and returned with syphilis to the Old. As in much early colonial trade, Europe got more than it gave.

The history of syphilis is a complex drama involving the rise and fall of kings, changing governments and devastating wars. The final act was to have been played in 1943, with the general introduction of penicillin. It was a "magic bullet"; cases of reported syphilis plummeted. The words "and syphilology" were dropped from the title of the *AMA Archives of Dermatology and Syphilology*. By the mid-1950's hospitals were no longer required to do routine admission serological tests for syphilis to become accredited. A generation of physicians were trained without seeing syphilis in all its protean manifestations. It was no longer the case, as it had been in Osler's time, that to know syphilis in its many manifestations and variations was to know clinical medicine.[1]

But syphilis flourished in neglect. Its resurrection was abetted by increasing promiscuity, a relatively simple therapy and a loss of detective diagnostic skill. Because syphilis had been "conquered," the federal government withdrew funding for US Public Health Service (USPHS) epidemiologic studies and case finding.[2]

In the early 1970's there were 23,000 cases of infectious syphilis per year reported to the USPHS. A conservative estimate has it that for every case reported, nine are not. This implies almost a quarter of a million new cases of syphilis per year in the United States.[3] There is still a great deal of syphilis for primary physicians to recognize, understand and treat.

Pathophysiology

Syphilis may have lessons to teach us in this modern immunologic era of medicine. Consider this most unusual infectious disease: An organism, the delicate spirochete *Treponema pallidum*, is no longer than a red blood cell. It is exquisitely sensitive to drying, heat and air. Yet it can infect

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ABBREVIATIONS USED IN TEXT

FTA-ABS = fluorescent treponemal antibody absorption (test)
TPI = *Treponema pallidum* immobilization (test)

a human being anytime from the fourth month of intrauterine life to old age. It may affect any system and can remain destructive for the victim's entire lifetime. Or it may lie dormant for a quarter century or more, living in harmless parasitism with its host.

At its worst, it is a prolonged infectious polyvasculitis with immunopathologic overlay; at best, it is an inconvenient or embarrassing blood test result.

In the overwhelming majority of cases, the disease is transmitted by sexual activity. Transmission of the treponeme can occur through mucous membranes, minutely abraded skin or, some believe, by way of normal hair follicles. Entering through the dermis, the spirochetes seed rapidly into the lymphatics and from there enter the bloodstream to disseminate throughout the body. Invading the perivascular lymphatics of multiple organs, the treponemes stimulate a cellular inflammatory response to granulomata formation and proliferation in the intima of the vasa vasorum. The resulting decrease or loss of blood supply by tissues served by the injured vessels may lead to necrosis. Eventually, the acute inflammation is replaced by fibrous scar tissue.

T pallidum organisms may episodically, in the early stages of disease, break out again as spirochetemia. Or they may assume an intracellular sequestration in multiple tissues, protected by the cell, some think, from antibodies and antibacterial agents.[4]

The antibody response to the treponemes may be itself immunopathologic. Immune-deposit disease in syphilis so far has been documented in the kidneys.[5-7]

In later stages, tissue hypersensitivity to *T pallidum* may become prominent, including proliferative fibrosis with hypertrophic masses, reactive tissue and necrosis—that is, formation of gummata.

Stages of Syphilis

Beginning in 1891, Boeck in Oslo studied 2,000 patients with untreated syphilis to determine the natural course of the disease. Studies of this population have continued to 1955[8] (Figure 1). The various stages of syphilis are discussed below (see Table 1).

Acquired Syphilis

Primary. The cardinal feature of the primary stage is the chancre, occurring at the site of inoculation within three months of the exposure. Most chancres begin as papules, then erode and become ulcerative. They are painless, indolent, punched-out lesions which have a scanty yellow discharge. They teem with spirochetes and are highly infectious. They may appear anywhere, although 95 percent are genital. They have been noted to occur in or around the mouth, anus, breast, rectum, cervix and colostomy stoma. Untreated, they heal spontaneously.

Secondary. Generally this stage is clinically manifest within six months of exposure. The chancre or chancres may still be present but are usually healing. This stage has protean manifestations, but four major syndromes have been seen: (1) a constitutional, *flu*-like illness; (2)

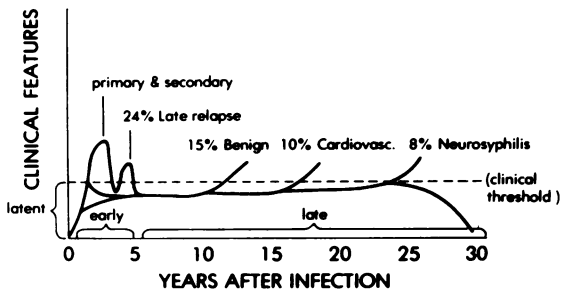

Figure 1.—Results of studies of the course of untreated syphilis in 2,000 patients.

TABLE 1.—*The Stages of Syphilis*

ACQUIRED SYPHILIS
Primary
Secondary
Latent
Early latent
Late latent
Tertiary
Late benign syphilis
Cardiovascular syphilis
Neurosyphilis
Meningovascular syphilis
Aseptic meningitis
Tabes dorsalis
Preataxic
Ataxic
Paralytic
General paresis of the insane
Latent neurosyphilis
CONGENITAL SYPHILIS

generalized lymphadenopathy with or without splenomegaly; (3) rash, involving skin and mucous membranes, and (4) visceral involvement, such as hepatitis, nephritis, osteitis or gastritis.

The secondary stage is also infectious and, like the primary, will resolve without therapy.

Latent. Latent syphilis is hidden. By definition, there are no clinical manifestations.

Early latent is that period, generally two to four years from infection, during which spontaneous clinical relapse may occur, with resumption of spirochetemia and, usually, a secondary lues-like condition. During the four years following inoculation, the victim remains an epidemiologic threat because secondary lues is infectious. In almost a quarter of untreated patients this clinical recrudescence will occur.

Late latent is that stage of the disease after the fourth year from infection when the victim is no longer contagious but remains host to living treponemes.

In two thirds of untreated people, spirochetes and host will live amicably together until the patient dies of other causes. In about a third, however, the organism will continue to act upon the host to cause a variety of mischief—or, tertiary syphilis.[8-10]

Tertiary. Late benign syphilis occurs in about 15 percent of untreated victims. Gummata are its cardinal feature. A gumma seems to represent a proliferative reaction in which, though the patient appears to be in a latent state, there is chronically progressive inflammation and fibrosis. This may, depending on the organ involved, leave such severe scarring as to result in a pronounced disturbance of the affected tissues.

A gumma may undergo central necrosis, with breakthrough of the wall of the lesion, which then drains by way of one or more sinuses. Any tissue may be involved but the most frequently affected are bone, skin and upper respiratory tract.

Cardiovascular syphilis complicates the lives of about 10 percent of untreated sufferers. Osler[11] described the basic lesion of all syphilis in all stages and all organs as an endarteritis. It is within this category of tertiary lues that the truth of his observation is most evident. The basic lesion of cardiovascular syphilis is aortitis, with its pathological potential for aortic insufficiency, coronary vessel osteitis and ischemia, and the highly questionable entity of infective myocarditis.

Neurosyphilis affects some 8 percent of untreated persons. The classic manifestations of this late-stage involvement are tabes dorsalis and the general paresis of the insane. Active meningovascular syphilis is more commonly associated with secondary than with tertiary involvement.

Congenital Syphilis

A child born to a syphilitic mother may acquire the disease by transplacental transmission of *T pallidum.* Because the organism does not cross the placental barrier until the 16th to 19th week, early detection and therapy of the pregnant woman is effective.[12,13]

In untreated women, 25 percent of infected infants die in utero. Another 25 percent will die shortly after birth. In about 40 percent of the infants that survive—if untreated—symptomatic syphilis will occur, with developmental retardation, ocular, dental, neurological, bony, articular or visceral lesions all possible.[14]

Review of Systems

It has been said that syphilis, the great imitator, can look like anything. But if that is true, a clinician can have no discrete reason to suspect syphilis in any single circumstance. It must, then, be kept as a differential diagnosis to be considered in almost all cases. To illustrate this, it is useful to approach the disease from the point of view of systems, as one would do in ordinary history and physical examination, rather than reviewing the constellation of symptoms and signs in each stage; the latter all tend to merge and cross over anyway.

General

Puniness and growth retardation are features of congenital lues. Fever may accompany any stage of the disease but is most prominent in the malaise of secondary lues. It may be mild and continuous or, in its most remarkable form, paroxysmal, with spikes up to 40.6°C (105°F). Fever may persist for months, and syphilis must be part of the differential diagnosis in evaluation of fevers of unknown origin. Loss of weight, anemia, lymphocytosis and elevated erythrocyte sedimentation rate may be part of secondary syphilis. In the later stages, constitutional symptoms may be in consequence of the compromise of specific organs, as in the fatigue of luetic aortic insufficiency.

Nodes

Nodes neighboring the primary chancre may enlarge, growing hard and nontender. A more generalized lymphadenopathy is common in sec-

ondary syphilis, with pronounced involvement of epitrochlear and posterior cervical nodes. These enlarged nodes are rubbery and painless. Abdominal examination may show splenomegaly in this stage, and the lymphadenopathy may be so impressive as to be mistaken for mononucleosis—which secondary syphilis much resembles. More serious errors have been made as in the several reported instances in which patients narrowly escaped total nodal irradiation for putative Hodgkin disease, a misdiagnosis of their secondary lues.[15,16]

Skin

It is the skin that is the great mirror of luetic involvement and the organ on which we rely most for the diagnosis of syphilis. However, it may also be the most deceptive because it is in this area—even more than elsewhere—that the great imitator justifies its reputation for deceit.

In addition to the already described chancres of primary disease, cutaneous lesions are most common in the secondary stages of the disease. *Macular syphilid,* or syphilitic roseola, is most prominent on trunk and arms, often sparing the face. The symmetrically arranged macules are reddish-brown, persist for one to two weeks and may undergo multiple relapses. *Papular syphilid* may look like acne; a *pustular* rash resembles smallpox, or a *squamous syphilid* looks like psoriasis.

While syphilitic rashes may look like a variety of skin diseases, they have certain characteristics in common. They are often generalized, painless and nonpruritic and have a predilection for the palms and soles. The lesions are more commonly discrete than confluent and are sharply demarcated; and, like a reverse bull's-eye, the color becomes more intense as one proceeds from periphery to center.

Mucous patches are found in most areas of skin, such as perineum, groin or angle of mouth. They are flat, warty outgrowths with well-defined margins and surfaces covered with greyish secretions. They are highly infectious.

Gummata may affect any portion of the skin and leave scars as they involute or create ulcers as they break down. Because caseation occurs, gummata may be mistaken for tuberculosis.

Condylomata lata are highly infectious hypertrophied papillae of the perianal or perivulvar skin. They must be distinguished from the more common, virally induced condylomata acuminata.

Patchy alopecia or general thinning of the hair may occur in acquired lues, and the hair of head or eyebrows may fall out in the congenital form of the disease.

Syphilitic onycholysis is rare in other than congenital lues, though the nails may fall out entirely in severe secondary syphilis.

Head

Frontal, maxillary and mandibular bossing from periostitis of the skull are classic features of congenital lues. The saddle nose, with snuffles, of congenital disease occurs when syphilitic perichondritis erodes and collapses the nasal septum. The nose is also a favored spot for gummata.

Ears

Deafness may occur early in congenital lues, but has been reported to present as a Meniere-like condition in young adulthood[10] or from isolated VIII nerve failure in later neurosyphilis.

Mouth

In the oral cavity, the examiner may see chancres, glossitis, mucous patches, gummata, pharyngitis and palatal perforation from periostitis or the gummata. Hutchinson teeth (screwdriver-shaped secondary incisors) and mulberry molars (with supernumerary or defective cusps) are classic features of congenital disease.

Eyes

Ocular lesions include interstitial keratitis, iritis (occurs mostly in secondary syphilis, affecting one eye before the other, generally three to six months after the chancre), choritis and retinitis. The pupillary changes of tabes dorsalis are easy to remember: The Argyll-Robertson pupil may accommodate but does not react to light. Blindness may be a consequence of either optic nerve damage or inflammatory changes in other structures of the eye. Optic atrophy, ptosis and ophthalmoplegias have all been reported.

Neck

Gummata may involve the larynx, leading to misdiagnosis as cancer or tuberculosis. More urgently, such a mass may cause scarring and stridor. The hoarse "syphilitic cry" of congenital lues is probably due to laryngeal involvement.[9]

Breasts

Osler mentions syphilitic mastitis, with unilateral chronic diffuse induration or local nodules.[11] Axillary nodes may be involved, and the differ-

ential diagnosis from cancer of the breast may be difficult.

Chest

A gumma may involve the trachea, with bronchial dilatation below the lesion. Symptoms are those of obstruction, with dyspnea, stridor, cough and prolongation of inspiration. Rarely, tracheoesophageal fistulas may occur. Syphilitic pneumonia has been reported in congenital lues. Gummatous disease of the lungs, which is very uncommon, may resemble tuberculosis or fibrotic lung disease.[9]

Heart

Syphilitic endocarditis has not been described, though a nonbacterial thrombotic (marantic) endocarditis may coexist. Syphilitic myocarditis has been suspected on the basis of clinical findings, electrocardiogram and response to therapy during the spirochetemic phases of early lues. Still, this disease entity remains very much in doubt.[9]

Gummatous myocarditis, though very rare, has been recognized. Most gummata are in the left ventricular wall and may be associated with bundle branch block on electrocardiogram. Interventricular septal gumma may cause complete heart block[17] and, most uncommonly, a gumma may obstruct one or more coronary ostia.

Syphilitic aortitis is the basic and most frequent lesion of tertiary lues. During the spirochetemia of early disease, treponemes invade the aortic wall, probably by way of the vasa vasorum. An obliterating endarteritis follows, generally in the first portion of the aortic arch. Diffuse dilation or saccular aneurysm results. Dilatation of the aortic root separates the valve leaflets, with resultant aortic insufficiency. Inflammation of the wall may extend to involve the coronary ostia. Should they become occluded, myocardial ischemia or infarct may follow.

Symptoms may also arise from the simple mass effect of the aneurysm, which may compromise any of the mediastinal structures, including the trachea, bronchi, lungs, esophagus, vagus, cervical sympathetic nerves or the recurrent laryngeal nerve. The pulsatile mass may erode through adjacent ribs or spine. These aneurysms do not dissect, but they may rupture.

Abdominal aortic aneurysms are about a tenth as frequent as thoracic ones, and those of syphilitic origin are characteristically above the level of the renal arteries, in contrast to aneurysms of atherosclerotic origin, which are generally at or below this level. The syphilitic aneurysm may lie high under the diaphragm.[18]

Gastrointestinal

Hepatosplenomegaly is a common associate of congenital lues. The liver shows fibrosis and large numbers of spirochetes. Clinical jaundice, hepatomegaly with tenderness and increased levels of transaminase with a disproportionate rise in alkaline phosphatase, are the hallmarks of the syphilitic hepatitis of the secondary stage of disease. A liver biopsy specimen in syphilitic hepatitis will show portal inflammation, polymorphonuclear leukocytes surrounding bile ducts and necrotic areas extending from portal triads to central veins. Whether the spirochetes themselves can be seen in the liver tissue is a subject of dispute. Hepatic gummata may occur in tertiary disease and, with necrosis and scarring, lead to the classic hobnail liver of late syphilis.[11,19,20]

Acute esophagitis and erosive syphilitic gastritis may occur, the latter involving pain, vomiting, weight loss and hemorrhagic inflammation of the stomach on endoscopy. *T pallidum* may be demonstrated in biopsy material obtained from the gastric mucosa.[21]

Gummata of the esophagus may be mistaken for esophageal carcinoma, or the great imitator may present as pyloric obstruction, linitis plastica, or another intra-abdominal gummatous mass. Osler mentions the possibility of pancreatitis and jejunitis from syphilis. If these are luetic entities, they are rare.[11]

Rectal lues may manifest as chancres, and, as these are sometimes multiple, they may appear as a condition resembling ulcerative colitis, especially in homosexual men.[22]

Gummata should remain in the differential diagnosis of adenocarcinoma of the colon.

Genitourinary

In addition to genital chancres, the urinary tract has been variously involved by syphilitic lesions. Clinically, the most common manifestation of renal involvement is mild proteinuria, which may occur in secondary lues. A full-blown nephrotic syndrome accompanies secondary syphilis in some cases.[5] IgG immune complexes—treponemal antigen and antibody reactions—can be shown along the glomerular basement membrane.[6,7] The nephrosis remits with either treponemocidal therapy or the simple passage of time. Hemorrhagic

nephritis, indistinguishable on biopsy from that classically associated with poststreptococcal glomerulonephritis, is an uncommon but very serious complication which may progress to azotemia and death.[5] Paroxysmal cold hemoglobinuria may occur with congenital or acquired lues.[23] Muscle cramps, headache, fever and hemoglobinuria precipitated by cold will, in this case, respond to antisyphilitic therapy.

Prostatic and bladder gummata are rare and syphilitic orchitis rarer still. A neurogenic bladder may occur as a feature of neurosyphilis.

Extremities

Arthritis may occur at any stage of syphilis and may be so acute as to be mistaken for rheumatic fever. Or it may be chronic, with neuropathic painless destruction of joints. Arthritis of any sort is usually symmetrical.[13,14]

The Clutton joint of congenital lues involves hydrarthrosis, frequently bilateral, secondary to syphilitic synovitis with involvement of bone or cartilage. The Charcot joint of tertiary syphilis is neuropathic, that is, painless, with thickened synovium and cartilagenous injury. Most frequent in the knees, it may occur in the ankles or lumbar spine as well.

Bony lesions are part of both congenital and acquired lues. Periostitis, perichondritis, sclerosing osteitis, lytic lesions, gummata and bursitis have all been seen. Almost any bone, including the axial skeleton, may be involved.[24]

It is periostitis of the tibiae in congenital lues that produces the peculiar conformation called "sabre shins."

Osler noted syphilitic myositis in gastrocnemius and sternocleidomastoid muscles. On histological section, an affected muscle specimen shows vasculitis and interstitial myostis.[11]

Central Nervous System

The central nervous system may be involved in any stage of syphilis. There are four cardinal clinical categories.

Meningovascular syphilis is a manifestation of early lues, occurring within the first four years after primary infection. It presents as an aseptic meningitis, with headache, irritability and mental fatigue. Ocular features are common, often with remarkable variation from time to time. Pupils may be unequal or irregular and, although abnormal pupils have been noted in most patients with neurosyphilis, true Argyll-Robertson pupils are rare.[25] Ptosis, extraocular muscle palsies and optic neuritis have all been described.[11,26] Sudden, violent delirium, changes of character, prolonged stupor or coma, convulsions and major vascular occlusive events may complicate the picture. Studies of cerebrospinal fluid commonly show a positive VDRL result, increased protein and pleocytosis. A milder, transient aseptic meningitis sometimes accompanies secondary syphilis.

Tabes dorsalis is a neuropathy of late syphilis, in which there is degeneration of the root fibers of the posterior columns, spinal ganglia, cranial and peripheral nerves. There are three stages as follows: (1) in the *preataxic* stage, tabetic crises may occur involving lightning pains of the legs and trunk that last one to two seconds and follow the path of the dorsal nerve roots. Loss of pain and temperature sensation are concurrent. Ocular neuropathies, bladder symptoms, loss of deep tendon reflexes, deafness and paralysis of the vocal cords may follow. (2) The *ataxic* stage of tabes occurs when afferent impulses are lost, leading to incoordination and muscle hypotonia. Visceral crises, akin to pain crises, sometimes occur in this stage; gastric crises include severe epigastric pain, nausea, vomiting, hematemesis and, sometimes, death. The blood pressure may be very high, and the condition has been said to be associated with mesenteric vasospasm. Laryngeal crises may lead to sudden death; and even uncontrollable sneezing fits, the nasal crises, have been said to be tabetic in origin.[27] (3) After many years, the *paralytic stage* supervenes. The patient becomes bedridden and paralyzed, eventually dying of infection.

General paresis of the insane is a chronic luetic meningoencephalitis characterized by mental changes, dementia and paralysis. Irritability, changes in character, tremor, seizures, eye changes and hemicranial headaches may precede a hypomanic phase during which delusions of grandeur govern. Speech eventually becomes slurred, with syncope and paralysis thereafter. Death may occur during seizures, or a chronic dementia may persist for years.

Latent neurosyphilis has no signs or symptoms, but the cerebrospinal fluid has a positive VDRL.

In the modern era, classic tabes and general paresis are rare and are being replaced by atypical and in-between forms.[26] The nontreponemal serological tests for syphilis may be negative in as many as 40 percent of patients with neurosyphilis,[28] and the assumption that the serum fluores-

cent treponemal antibody absorption (FTA-ABS) test in serum is always positive has not held up.[29] For general purposes, however, a positive cerebrospinal fluid VDRL defines neurosyphilis, while cerebrospinal fluid pleocytosis and elevated protein level define its activity.

Laboratory Diagnosis

The laboratory tests for syphilis may be simple or confusing, depending on one's approach. Though there are any number of serological tests, the most commonly used study is the VDRL, the most sensitive is the FTA-ABS and the most specific is the *Treponema pallidum* immobilization test.

VDRL stands for Veneral Disease Research Laboratory and is a flocculation test that depends on the cross-reactivity of antitreponemal antibodies in the serum of the victim to a cardiolipin extract from cow's heart. It is easy and cheap and, thus, may be used for screening large numbers of patients.

In primary syphilis, about 25 percent of patients will have a positive VDRL test within the first week of the appearance of a chancre, 50 percent in the second week and 75 percent in the third week following infection.[2]

In secondary syphilis, close to 100 percent of VDRL tests are positive.

One must be careful in congenital lues, as the VDRL—an IgG function—measured in the first three postnatal months is that of the mother, not the child.

With therapy, about 25 percent of patients treated within four years will remain serofast; 75 percent will become serofast if treated later, but titers may decline, providing useful information about the adequacy of treatment.[30]

In neurosyphilis, 50 percent to 75 percent of victims will have reactive serum VDRL tests and almost 100 percent will have reactive serum FTA-ABS tests.[26] As few as 57 percent will have reactive cerebrospinal fluid VDRL tests,[26] but the value of FTA-ABS tests in cerebrospinal fluid remains in doubt.[31]

Biological false-positive VDRL tests may occur in a number of circumstances as listed in Table 2. The titer of a biological false-positive result is generally 1:4 or less. However, in one study of patients with biological false-positive results persisting for more than six months, about half of them turned out to have syphilis.[32]

FTA-ABS is the fluorescent treponemal antibody-absorption test, in which serum from the patient is applied to a slide on which *T pallidum* organisms have been dried. Globulin antibodies in the victim's serum adhere to the treponemes. Fluorescein-tagged antiglobulin antibodies are overlaid on the slide. The globulin on the treponemes binds the tagged antiglobulin and the slide is then read. To increase specificity, the test serum is pretreated with absorption to nonluetic treponemes that remove antibodies nonpathogenic to spirochetes.

TABLE 2.—*Biological False-Positive VDRL Tests*

Acute
Viral infections: herpes, mononucleosis, hepatitis
Lymphogranuloma venereum
Vaccinations
Immunizations
Chronic
Age
Heroin addiction
Leprosy
Malaria
Collagen disease
Lymphoma
Familial
Nonvenereal treponemes
Yaws
Pinta
Bejel
Passive reaginemia
Placental transfer

False-positive tests have been shown in systemic lupus, rheumatoid arthritis, lymphosarcoma, alcoholic cirrhosis and pregnancy.[32-35] It has been said that there are morphological differences between false and true positives in systemic lupus, with false results showing beading of the fluorescein tagging on the treponeme rather than linear deposition.[35]

The FTA-ABS is the most sensitive of all tests, being 75 percent positive in the earliest lues and close to 100 percent persisting thereafter. Only the very earliest therapy of seronegative (that is, VDRL-negative) primary syphilis will cause the FTA-ABS, in about 75 percent of those so treated, to revert to negative.[36]

The TPI (*Treponema pallidum* immobilization) test is done by adding patient serum (potentially containing antibody) and complement to a suspension of living treponemes extracted from rabbit testes. The test is run under a dark-field microscope and scored for whether immobilization of the organism occurs. Antibiotic drugs taken by the patient will invalidate the test, which is technically difficult under the best of circumstances. It is far less sensitive than the FTA-ABS test but far more specific than any other laboratory investigation

short of staining the organism in tissue. It is not available in most hospitals but can be obtained through the Communicable Disease Center, Atlanta.

Diagnosis of Suspected Lues

After a complete history and physical examination, dark-field microscopic examination should be done on all suspected lesions. It is, however, a waste of time to do a dark-field study on lesions in the mouth, as normal oral treponemes may be present. If the VDRL test is insufficiently convincing for diagnosis, an FTA-ABS test should be done. A suggested approach is outlined in Figure 2.

Therapy

If syphilis is diagnosed, the nature of therapy depends on the stage of the disease (Table 3).

Studies show that a total dose of 6 to 9 million units of parenteral penicillin G results in a satisfactory clinical response in about 90 percent of patients with neurosyphilis.[37] Because living treponemes have been shown in aqueous humor and the central nervous system following supposed ablative therapy, and because neurological signs may continue to progress even with apparently adequate therapy, some clinicians will hospitalize patients with neurosyphilis, especially if the victim is symptomatic or has not responded to initial therapy. In the latter case, one may wish to increase the total dose of aqueous penicillin G to 12 to 24 million units given intravenously each day for ten days. It has been proposed that the 9.6 million unit standard dose, though spirochetocidal in blood, does not achieve adequate therapeutic levels in the CSF.[38]

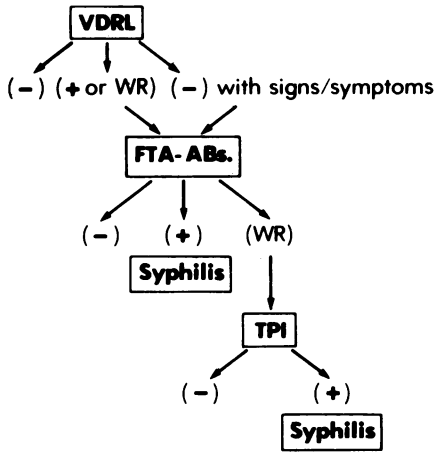

Figure 2.—Laboratory evaluation of suspected syphilis. (FTA-ABs = fluorescent treponemal antibody absorption [test]; TPI = *Treponema pallidum* immobilization [test]; VDRL = Venereal Disease Research Laboratory [test]; WR = weakly reactive.)

In case of syphilis of unknown duration, a cerebrospinal fluid VDRL test should be carried out if there are any symptoms suggestive of neurosyphilis because there may be a therapeutic difference. All patients should have repeat serological testing done 24 months after therapy. Careful follow-up is especially important in those treated with antibiotics other than penicillin, because the efficacy of these alternatives in late lues and, especially, in neurosyphilis is unproved. In a patient with established neurosyphilis, serological testing should continue for three years, with clinical and CSF examinations every six months.

Retreatment should be considered in the following situations: (1) when clinical signs or symptoms of syphilis persist or recur, (2) when there is a sustained fourfold increase in the titer of the VDRL test or (3) when an initially high titer for the VDRL test fails to show a fourfold decrease within a year.

The Jarish-Herxheimer reaction is so common

TABLE 3.—*Appropriate Therapy Depending on the Stage of Syphilis*

Stage	*Therapy*	*Serological Finding Without Therapy (Percent)*		
		FTA-ABS	*VDRL*	*TPI*
Congenital	50,000 units benzathine penicillin G/kg of body weight in single dose		↑ titers ×3 mos	
Acquired				
Primary (≤3 mos.)	2.4 million units benzathine penicillin G in single dose	85	25-75	55
Secondary (≤6 mos.)		99	97	94
Early latent (≤4 yrs.)	2.4 million units benzathine penicillin G every 10 days ×4 doses	95	74	94
Late latent (>4 yrs.)				
Late benign				
Cardiovascular				
Neurosyphilis	2.4 million units benzathine penicillin G every 10 days ×4 doses (see text)	95	74	94

FTA-ABS = fluorescent treponemal antibody absorption (test); TPI = *Treponema pallidum* immobilization (test)

an accompaniment of the therapy of syphilis that it deserves mention here. Nine out of ten patients with secondary and, to a lesser extent, other stages of syphilis will show a Jarish-Herxheimer reaction within several hours of their first dose of the antibiotic drug. The reaction is characterized by chills, fever, headache, muscle and joint pains. Skin lesions may become more prominent, more edematous and more brilliant in color. The reaction lasts several hours and does not recur following subsequent injections. It may be interpreted by the patient and unwary physician as an allergy to penicillin, and a careful history is required to distinguish between the two. The Jarish-Herxheimer reaction is thought to be due to the sudden release of large amounts of treponemal antigen, with subsequent antigen-antibody reaction in the host.

Summary

Syphilis, once thought a conquered disease, is still very much with us. Because many physicians are not familiar with its multitudinous manifestations and the changes in classic presentation induced by the ubiquity of antibiotics, syphilis remains a diagnostic and therapeutic challenge to the modern era. Osler was right.

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